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Kinetics of Lead in Bone and Blood after End of Occupational Exposure

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Abstract. In 14 retired lead workers, followed for over 18 years after end of exposure, repeated analyses of lead levels in finger bone by an *in vivo* X-ray fluorescence method revealed a decrease of lead concentration. The data were analysed using an exponential retention model. For the whole group the biological half-time was 16 (asymptotic 95% confidence interval, CI 12,23) years. The median of the estimated bone lead levels at the end of exposure was 85 $\mu g \cdot g^{-1}$ above the "background" (3 $\mu g \cdot g^{-1}$). A simultaneous follow-up of blood lead levels displayed a decrease, which could be described by a tri-exponential retention model with group half-times of 34 (CI 29,41) days, 1.2 (CI 0.9,1.8) years, and 13 (CI 10,18) years, respectively. The median of the estimated blood lead levels at the end of exposure for the three components were 0.49, 0.61, and 1.1 $\mu mol \cdot l^{-1}$ above the "background" (0.38–0.56 $\mu mol \cdot l^{-1}$), respectively. The well-documented decrease of lead exposure in the general population over the years, urged the use of a decreasing "background" of blood lead during the time of the study. The slowest of the three components represented the skeleton (probably mainly cortical bone), as did mainly probably also the intermediate one (trabecular bone). The data show the rather slow turnover of lead in the skeleton, the usefulnes of *in vivo* skeletal lead measurements as a long-term exposure index, and the importance of bone as a source of "endogenous" lead exposure.

For thousands of years lead has been widely used, and the study of lead is of utmost importance because of its known toxicity. Excess exposure may result in serious consequences, if the tissue concentrations reach critical levels.

The main part of human lead uptake takes place via the gastrointestinal and respiratory tracts. In work places where lead is handled, exposure primarily takes place via inhalation. In addition, lead workers are often further exposed by consumption of tobacco, snuff, and food and beverages, contaminated with lead from the work environment.

A large part of the absorbed lead is incorporated in the skeleton (Gusserow 1861; Barry 1975), which contains more than 90 percent of the body burden of lead (Barry 1975).

Thus, there is a great need for kinetic studies of this large lead pool. However, very little data based on direct measurements in humans are available. The turnover of lead in the human body has often been assumed to be rather slow (Task group on metal accumulation 1973). Several estimations of the turnover rate of lead have been made, based upon: 1) animal studies, 2) bone remodelling studies in humans, 3) various lead balance models, and 4) observation of the decrease in blood lead levels after end of occupational exposure. The half-times reported for lead in bone or whole body have varied considerably, from a few years and up to more than one hundred years.

Yet another possibility is to measure lead directly *in vivo* in the skeleton. We have earlier reported a mean half-time of seven years for lead in finger bone, based on such measurements (Christoffersson *et al.* 1986), and the same mean half-time was observed for the slow component of blood lead (Christoffersson *et al.* 1986). These data resulted from a longitudinal study of retired lead workers; the follow-up time (from end of occupational exposure) was between 1.7 and 13.4 years.

The possibility to accurately assess the kinetics of lead in a slow pool, such as the skeleton, is directly dependent upon follow-up time. The longitudinal study of this group of retired lead workers has therefore been continued and the follow-up time is now between 7.2 and 18.5 years. This paper reports the results of this study.

Materials and Methods

Subjects studied.

Group A. Starting during 1979–1982, a group of eight persons was studied. This group consisted of seven retired smelter workers and one former storage battery worker. The first bone lead measurements were made within 2–359 (median 47) days after the end of occupational exposure to lead. At the end of exposure the median age of the group was 64 (range 49–65) years and the median exposure time 25 (range 10–38) years. The members of this group were followed for 7.2–10.8 (median 9.8) years and the number of bone lead measurements for each individual was in the range 11–17 (median 13).

Group B. From 1971, six former storage-battery plant workers were studied. The first bone lead measurements were made 6.8–7.0 (median 6.9) years after the end of occupational exposure to lead. At the end of exposure their median age was 53 (range 30–65) years and the median exposure time 30 (range 3–45) years. The total follow-up time was 13.2–18.5 (median 17.7) years and the number of bone lead measurements for each individual ranged 7–13 (median 12).

(A summary of the characteristics of individuals is given in appendix 1.)

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All subjects gave their written consent and the project was approved by the Ethical Committee of the Lund University.

In vivo determination of finger bone lead, bone-Pb. *In vivo* measurements of bone lead were carried out using an X-ray fluorescence (XRF) method originally developed by Ahlgren *et al.* (1976) and Ahlgren & Mattsson (1979), and later improved by Christoffersson *et al.* (1986).

The content of lead was estimated from a measurement of the midpart of the second phalanx of the left forefinger. The finger was fixed in a polymethyl methacrylate holder and about 1 cm^3 of bone tissue was irradiated by two oppositely directed, collimated ^{57}Co sources, which emit two gamma-rays, 122 keV (87%) and 136 keV (10%), above the K-edge of lead, 88 keV. The total activity was about 0.6 GBq. The count rate of the produced characteristic lead Kα X-rays ($K\alpha_1$ = 75.0 keV and $K\alpha_2$ = 72.8 keV) was measured at a mean angle of 90° to the incident gamma-rays by means of a high purity, planar germanium detector (16 mm diameter × 5 mm) (fig. 1).

The observed count rate was converted to a bone lead concentration by using finger-like phantoms (Ahlgren & Mattsson 1979). These phantoms consisted of an inner core of silica paraffin wax and bone ash, with known amounts of lead added. The outer part of the phantoms consisted of silica paraffin wax, simulating the surrounding soft tissue. The count rate in the observed Kα peaks is, due to the short distances in the used geometry, dependent on the volume (diameter) of the bone examined. For typical diameters, 6–9 mm, of the bony part and for a bone mineral content of at least 20% (by wet weight), the bone mineral concentration is of less influence on the Kα count rate (Ahlgren & Mattsson 1979). Thus, the *in vivo* measurements were compared with measurements of the described finger-like phantoms having a bone mineral content of 20% (wet weight) and different diameters of the bone-simulating part. To estimate the dimensions of the phalanx studied *in vivo*, two radiographs of the finger phalanx, in orthogonal directions, were used.

In the 1978 measurements, a different detector, different collimators, and slightly different calibration procedures were used. The results from these measurements have been recalculated using the same calibration technique as in 1979–1990.

The measuring time (live) for an *in vivo* analysis was 1,800–2,000 sec., giving a minimum detectable concentration (MDC) of lead in the finger bone of approximately 20 μg lead per gram wet bone ($\mu g \cdot g^{-1}$), corresponding to three standard deviations above the background.

The absorbed dose to the centre of the finger and to the skin was 1 and 3 mGy respectively. The energy imparted was about 0.01 mJ, which gave a mean whole body dose equivalent of approximately 0.1 μSv. This is about 1000 to 10000 times lower than an ordinary X-ray examination.

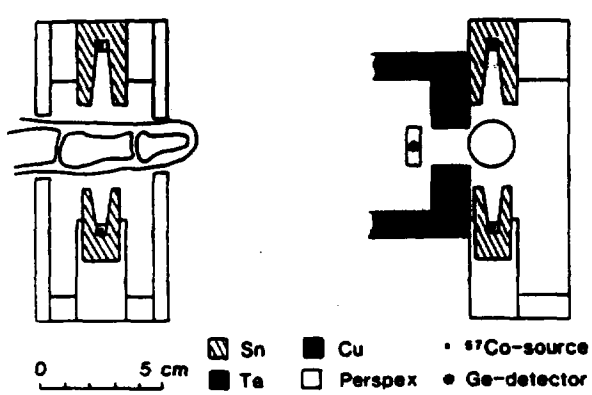

Fig. 1. The source and detector assembly used for *in vivo* X-ray fluorescence measurements of finger bone lead.

The reproducibility of this XRF method has previously been reported to be 10 μg·g⁻¹ (SD of differences, 15% of the mean) (Christoffersson *et al.* 1984) based on paired measurements on subjects with measured concentrations in the range 27–122 μg·g⁻¹ (mean 70) and 11 μg·g⁻¹ (SD of differences, 21% of the mean) Somervaille *et al.* (1989) based on paired measurements on six subjects with measured concentrations in the range < 20–104 μg·g⁻¹ (mean 49).

The accuracy of the method has earlier been verified by *post mortem* analysis of the second phalanx of the left forefinger from one subject, who had previously been measured *in vivo* (Christoffersson *et al.* 1984).

To further investigate the degree of accuracy of this *in vivo* XRF method, *post mortem* analysis using XRF and flame atomic absorption spectrometry (AAS; Schütz *et al.* 1987a) of one forefinger phalanx and one toe phalanx were made. These two subjects had earlier been analysed *in vivo*, and the time between the *in vivo* and *post mortem* analysis was about 6 months in both cases. In addition, *post mortem* analysis of three second forefinger phalanxes were made using XRF and AAS (in these cases no *in vivo* determinations had been made). The *post mortem* XRF analysis of the naked phalanxes were made using the same geometry as for the *in vivo* analysis. The lead concentration was estimated by using the quotient of Kα X-rays and incoherently scattered radiation (Ahlgren *et al.* 1981). The phalanxes were then cut into three pieces (proximal, middle and distal) of about equal length and analysed by AAS.

To estimate the type of bone (cortical-trabecular) at the site of measurement, the calcium (Ca) concentrations of the phalanxes were determined using AAS (Schütz *et al.* 1987a).

Determination of blood lead, blood-Pb. To determine the blood lead levels, blood-Pb, venous blood was obtained in metal-free heparinised tubes, at least in connection with each bone-Pb measurement, generally more often. The same analytical procedure was maintained during the whole study period. The samples were wet-ashed and the lead was complexed with dithizone, extracted and determined by AAS. Duplicate determinations were always made. The detection limit was 10 $\mu g \cdot l^{-1}$ (0.05 $\mu mol \cdot l^{-1}$; 1 $\mu g \cdot l^{-1}$ = 0.0048 $\mu mol \cdot l^{-1}$). The precision, calculated from duplicate determinations and expressed as the coefficient of variation (CV), was 2.8% in the range above 400 $\mu g \cdot l^{-1}$ (mean 536 $\mu g \cdot l^{-1}$; n = 50), 2.6% in the range 200–400 $\mu g \cdot l^{-1}$ (mean 307 $\mu g \cdot l^{-1}$; n = 100), and 3.5% in the range below 200 $\mu g \cdot l^{-1}$ (mean 151 $\mu g \cdot l^{-1}$; n = 81). For the lowest range, the precision for the last five year study period was identical to that for the whole period.

The accuracy was checked twice each year in an inter-Nordic laboratory calibration program. Our results averaged 97% (range 82–113%) of the mean. There was no time trend in our relative results.

Other examinations. For each individual, an occupational and medical history was recorded. Thirteen subjects had been temporarily removed from lead work because of excessive exposure (blood-Pb levels ≥ 3.5 $\mu mol \cdot l^{-1}$ or high urinary δ-aminolevulinic acid levels). One subject had a clinically silent chronic lymphatic leukaemia and another had a slight type 2 diabetes.

Venous blood samples were analysed at least once for haemoglobin level, as well as for calcium, phosphate and creatinine concentrations, and alkaline phosphatase and gamma-glutamyl transferase (S-GT) activities in serum. S-GT was raised in two subjects, both of whom were known to abuse alcohol. All other tests were within the reference limits.

Analysis of measured bone-Pb and blood-Pb concentrations.

Mathematical analysis. The analysis of the experimental retention

data made use of an extended version of the computer program EXPFIT (Guardabasso et al. 1989, Guardabasso, personal communication), which provides a simultaneous fit of a family of exponential curves.

The mathematical expression of exponential elimination curves used in the retention model can be written as

$$C_{Pb}(t) = \sum_{i=1}^{n} C_i \exp^{-\lambda_i t},$$

where t is the time after end of exposure, $C_{Pb}(t)$ is the lead concentration in bone (or blood) at time t, n is the number of exponential terms ($n \leq 4$), λ_i is the elimination rate for exponential term i, and C_i is the concentration at time zero corresponding to exponential i. The parameters (C_i and λ_i) and their asymptotic standard errors were estimated by using a modified Gauss-Newton algorithm, which minimises the unweighted residual sum of squares. Assuming asymptotic normality of the estimates, 95% confidence intervals (CI) were calculated. The estimated elimination rates, λ_i, and the corresponding CIs were transformed and presented as half-times, T_i.

The execution of the program EXPFIT requires that the number of exponential terms be specified and, for data sets containing more than one individual, whether the parameters C_i and/or λ_i are forced to be shared. This gives a higher weight to individuals for which there are many measuring points. However, in our case the number of measurements was about the same for all individuals (appendix 1 and 2). In general, in our estimations, C_i's were unconstrained and λ_i's were either unconstrained (for individual fits), or forced to be shared within group A, group B, and group A + B. In the following, the estimated half-time for a group of individuals is called shared half-time.

Bone-Pb. When a measured bone-Pb concentration was below the detection limit of 20 $\mu g \cdot g^{-1}$, a value of 10 $\mu g \cdot g^{-1}$ was assigned.

From all measured bone-Pb concentrations ≥ 20 $\mu g \cdot g^{-1}$, a constant "background" concentration of 3 $\mu g \cdot g^{-1}$ was subtracted prior to mathematical analysis. This value corresponds to the median concentration found in the femur of non-occupationally exposed Swedes (3.2, range 2.4–4.9 $\mu g \cdot g^{-1}$; n = 5; Gerhardsson *et al.* 1987).

Blood-Pb. An estimated decreasing "background" concentration dependent on calendar year was subtracted from all measured blood-Pb concentrations prior to the retention modelling.

This "background" was based on studies of blood-Pb levels in 1,773 Swedish children during 1978–88 (Schütz *et al.* 1989) and 166 non-occupationally exposed Swedish adult men in 1984 (Svensson *et al.* 1987). The "background" in each year was calculated from a mean of 0.35 $\mu mol \cdot l^{-1}$ observed for the men in 1984, assuming a constant yearly decrease of 0.016 $\mu mol \cdot l^{-1}$ (estimated from the children's data). The "background" thus varied from a maximum of 0.56 $\mu mol \cdot l^{-1}$ in 1971 to 0.25 $\mu mol \cdot l^{-1}$ in 1990.

For subjects with too few blood-Pb determinations in the time period immediately after end of occupational exposure (less than four during the first two months) to provide a meaningful estimate of the fast component, this component was assumed to have a half-time of 30 days, which is the median value of a larger material (Schütz *et al.* 1987b). This was not necessary in the shared group analyses.

The different estimations were compared by computing F-ratios to test the difference in sums of squares adjusted for the number of parameters.

Results

Bone-Pb

For all samples, there was a good correlation between the *post mortem* XRF and AAS analyses, especially considering that the measurement volumes were not necessarily the same

Table 1

In vivo and *post mortem* analysis of forefinger phalanxes (XRF = X-ray fluorescence, AAS = atomic absorption spectrometry). All concentrations by mass wet weight. The indicated uncertainties (± S.D.) are due to counting statistics only.

		Bone-Pb ($\mu g \cdot g^{-1}$)			Bone-Ca ($mg \cdot g^{-1}$)
ID	Section	*In vivo* XRF	*Post mortem* XRF	AAS	AAS
A-3	Proximal	–	40 ± 5	47	122
	Middle	27 ± 14	40 ± 3	36	168
	Distal	–	48 ± 4	60	156
B-1	Proximal	–	–	135*	114*
	Middle	86 ± 16	119 ± 2*	–	–
	Distal	–	112 ± 2*	138*	125*
C	Proximal	–	71	90	129
	Middle	–	48	45	165
	Distal	–	64	77	149
D	Proximal	–	67	82	144
	Middle	–	62	61	211
	Distal	–	75	89	162
E	Proximal	–	65	69	137
	Middle	–	57	55	186
	Distal	–	85	87	153

* A toe phalanx (the *in vivo* measurement was made on the forefinger phalanx)

(table 1). The measured *in vivo* lead concentration in the finger phalanx (subject A-3) corresponded well to *post mortem* analyses (fig. 2). The toe phalanx (subject B-1), analysed *post mortem*, showed a relatively high bone lead concentration as did the finger phalanx analysed *in vivo*. In the middle section of the forefinger phalanxes, the mean Ca concentration was 183 (range 165–211) $mg \cdot g^{-1}$. The end sections showed lower Ca concentrations: proximal end:

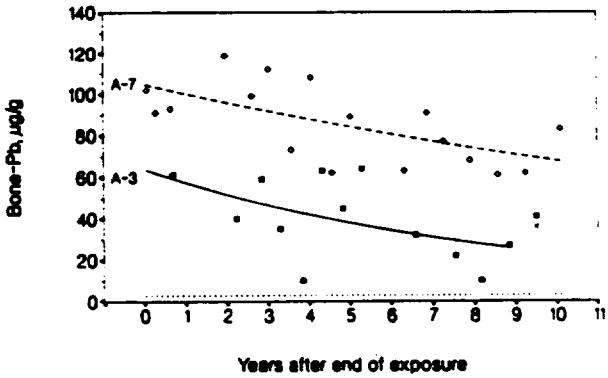

Fig. 2. Finger bone lead measurements and individually fitted mono-exponential curves after end of occupational exposure for subjects A-7 (○, estimated half-time 15 years) and A-3 (■, estimated half-time 6.2 years). Also indicated are the results of the *post mortem* analyses: X-ray fluorescence (■), atomic absorption spectrometry (×). The dotted line indicates the assumed "background" concentration (3 $\mu g \cdot g^{-1}$).

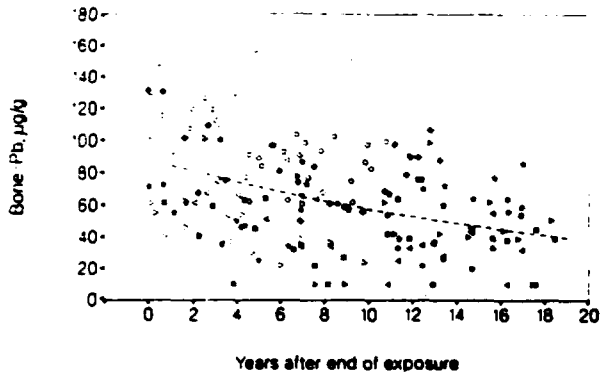

Fig. 3. Finger bone lead measurements after end of occupational exposure for groups A (open symbols, different subjects) and B (closed symbols). The dashed line corresponds to a mono-exponential retention model with the estimated shared half-time of 16 years and median intercept 85 $\mu g \cdot g^{-1}$. The dotted line indicates the assumed "background" concentration (3 $\mu g \cdot g^{-1}$).

mean 133 (range 122–144) $mg \cdot ^{-1}$, distal end: mean 155 (range 149-162) $mg \cdot g^{-1}$.

The finger bone-Pb concentrations decreased after end of exposure (figs. 2 and 3).

A mono-exponential retention model was used to explain the measured bone-Pb concentrations (appendix 1). No acceptable fits were achieved when applying a bi-exponential model to the individual measured bone-Pb concentrations.

The eight subjects in group A, followed for 7.2–10.8 years after end of occupational exposure, all showed estimated bone-Pb concentrations which decreased with time. The individually estimated half-times for bone-Pb were 6.2–27 years.

In group B, followed for 13.2–18.5 years after end of exposure, four of the six subjects had estimated bone-Pb concentrations which decreased with time. The individually estimated half-times were 11–470 years.

For groups A and B, the fitted mono-exponential elimination curves corresponded to a shared half-time of 13 (CI 10.19) and 37 (CI 14.∞) years, respectively. The half-times in group A and B did not differ significantly ($F_{1,15} = 3.73$; $P = 0.06$).

For all 14 subjects, the fitted mono-exponential elimination curve corresponded to a shared half-time of 16 (CI 12.23) years and the median of the estimated bone-Pb level at end of exposure was 85 $\mu g \cdot g^{-1}$ above the "background" (3 $\mu g \cdot g^{-1}$) (fig. 3).

Application of a bi-exponential shared retention model gave an acceptable fit for group A only. The estimated shared half-times were: $T_1 = 1.2$ (CI 0.5.∞) and $T_2 = 16$ (CI 9.3.59) years.

The values of the estimated elimination rates, λ_i, were not strongly dependent on the subtracted "background" bone-Pb concentration. Using "background" bone-Pb concentrations between 0 and 5 $\mu g \cdot g^{-1}$, it was found that the individually estimated elimination rates increased with 5–10% (except for subject B-3; 80% and subject B-5; 34%), and with about 5% for the shared group estimates.

Blood-Pb.

After end of occupational exposure, the blood-Pb decreased in a non-linear pattern (figs. 4 and 5). To explain the measured blood-Pb concentrations, bi- and tri-exponential retention models were fitted (appendix 2).

Using the bi-exponential model, 13 subjects showed estimated blood-Pb concentrations which in general decreased with time; for one subject, the estimated half-time was over 100 years. An acceptable fit was achieved for 4 of the 14 subjects when applying individual tri-exponential models.

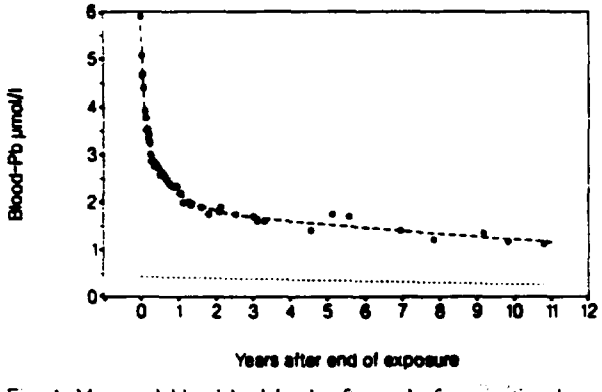

Fig. 4. Measured blood lead levels after end of occupational exposure for subject A-2. The dashed line indicates the sum of the fitted curves in a tri-exponential retention model: $T_1 = 22$ days, $T_2 = 0.48$ years, and $T_3 = 16$ years. The dotted line indicates the levels of the assumed linearly decreasing "background" concentration (in this case 0.25–0.43 $\mu mol \cdot l^{-1}$).

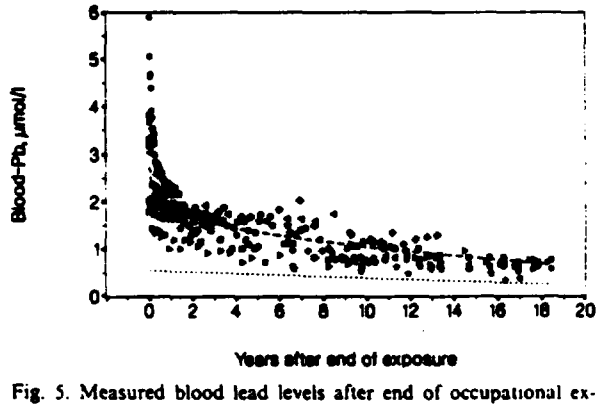

Fig. 5. Measured blood lead levels after end of occupational exposure for groups A (open symbols, different subjects) and B (closed symbols). The dashed line indicates the sum of the fitted curves in a tri-exponential retention model with estimated shared half-times of 34 days, 1.2 years, and 13 years and median intercepts from the shared model. The dotted line indicates the levels of the assumed linearly decreasing "background" concentration used for the members of group B (0.25–0.56 $\mu mol \cdot l^{-1}$).

In considering these 4 subjects in the tri-exponential model, and the other 10 in the bi-exponential one, the estimated half-time of the slowest component ranged 3.6–10 years.

On combining groups A and B, the shared tri-exponential model gave a better description of the data than the shared bi-exponential one ($F_{75,245} = 14.0$, $P < 0.001$).

For group A, the shared half-time for the slowest, third component was 12 (CI 9.3,16) years, for group B the corresponding value was 17 (CI 11,38) years. For the combined groups A and B, the estimated shared half-times were 34 (CI 29,41) days, 1.2 (CI 0.85,1.8) years, and 13 (CI 10,18) years and the medians of the estimated blood-Pb concentrations at end of exposure were 0.49, 0.61 and 1.1 $\mu mol \cdot l^{-1}$ above the "background" (0.38–0.56 $\mu mol \cdot l^{-1}$), respectively (fig. 5). A model allowing the third component to vary according to group A or B did not give a significantly better fit ($F_{1,244} = 0.75$, $P = 0.4$).

The use of a linearly decreasing, instead of a constant, blood-Pb "background" concentration mainly affects the slow component. For example, application of a constant blood-Pb "background" of 0.3 $\mu mol \cdot l^{-1}$ (Christoffersson *et al.* 1986) and computing shared half-times for all subjects, gives: $T_1 = 34$ (CI 29,41) days, $T_2 = 1.2$ (CI 0.8,2.1) years, and $T_3 = 9.8$ (CI 8.3,12) years.

Discussion

The data presented in this study clearly demonstrate that there is an elimination of bone-Pb after end of occupational exposure to lead, although it is rather slow.

The comparison between *in vivo* and *post mortem* XRF and AAS analyses showed a good agreement, strongly supporting the accuracy of the *in vivo* XRF method.

More than 18 years after end of exposure the detected bone-Pb levels were still generally higher than those found in "non-exposed" Scandinavians (Grandjean & Holma 1973; Lindh *et al.* 1978; Gerhardsson *et al.* 1987; Schütz *et al.* 1987a).

The shared half-time for bone-Pb is 16 years, with a narrow confidence interval, and is thus a fairly accurate estimate. However, there is a large difference in the estimates in individual subjects of the half-time for bone-Pb (range 6–470 years). Furthermore, four of the workers in group B showed estimated half-times, which seem to deviate from the rest: two of the workers had a very slow decrease, and two even showed an increase of the estimated bone-Pb concentration. There are several possible explanations.

The first measurements of bone-Pb in group B were made with a slightly different measuring set-up. This may have introduced a systematic error, which, however, should hardly exceed 10%, and which is probably not the reason for the observed difference.

The measurements of bone-Pb on the individuals of group B started about 7 years after end of occupational exposure, whereas the members of group A were followed from end of exposure. The lack of data during the first years after end of exposure, when the decrease in bone-Pb is relatively much larger, may influence the accuracy of the estimated half-times. This is indicated by the larger confidence intervals for the estimates for the members of group B.

The skeleton contains two types of bone tissue, cortical and trabecular. The turnover rate of trabecular bone has been reported to be three to ten times that of cortical bone (ICRP 1975). This is reflected in the turnover rate of lead, which has been reported to be faster in trabecular than in cortical bone (Rabinowitz *et al.* 1976; Schütz *et al.* 1987a). Thus, there is at least two different bone-lead pools in the skeleton.

Data on workers temporarily removed from exposure indicate that there exists no large, very rapid finger bone-Pb pool (Christoffersson *et al.* 1984).

According to Woodard & White (1986), the Ca concentration in pure cortical bone tissue is 22.5% (by wet weight) versus 7.4% in trabecular bone (assuming 33% cortical bone and 67% bone marrow, by mass). This elemental composition of bone tissues together with the mean of the measured Ca concentrations (table 1; 18.3% by mass), indicates that the site of measurement consists mainly of cortical bone (approximately 80% by mass). However, due to the design of the experimental set-up, it is realistic to believe that parts of the phalanx ends, with lower Ca concentrations, due to trabecular bone, also contribute to the signal.

The estimates obtained for the sum of two exponential curves for the bone-Pb in group A [$T_1 = 1.2$ (0.5,∞), and $T_2 = 16$ (9.3,59) years] indicate (in spite of the large CIs) the possibility of one slow and one faster lead pool, possibly representing trabecular and cortical bone, respectively. In group B the presence of two components may be obscured, due to the limitations set by the precision of the XRF technique and the lack of bone lead data during the first seven years after end of exposure.

Some of the present workers became old and the possibility of an effect on lead turnover from decalcification of the bone must be considered. Osteoporosis will probably tend to increase the elimination rate and thus decrease the half-time. Data showing a decrease in bone-Pb at high age may indicate such an effect (Wittmers *et al.* 1988). However, as there was no association between age and half-time in our material, it is unlikely that osteoporosis has severely affected our results.

The presented shared half-times of bone-Pb are somewhat longer than the ones presented earlier (Christoffersson *et al.* 1986) for the same two groups of individuals. However, in the latter case, the mean half-times were calculated by taking the mean of the individual λ_i's and no bone-Pb "background" was subtracted. Taking this into account, the results are fully compatible.

However, the present analysis has several advantages: The use of a program for simultaneous curve fitting means a refined analysis; it is possible to simultaneously analyse a group of data sets and thus to summarise all the information.

For blood-Pb, the shared half-time of about one month

for the rapid component in the shared model, dominating close to end of occupational exposure, is in excellent agreement with our earlier estimates (Schütz *et al.* 1987b).

As to the slow components in blood, we took into consideration that the "background" blood-Pb is decreasing in many countries, including Sweden (Schütz *et al.* 1989). If this factor is not considered, the decrease rate will be overestimated. As we had no detailed yearly information in adults, we used the levels over time in children, and adjusted the concentration to that found in adults. This is of course not optimal, but should be fairly accurate.

In the case of bone-Pb, there is no need to take into account a time trend, as this, if present, would be much delayed, as compared to blood. Also, the impact of the "background" is far less important, as indicated by calculations with different realistic "backgrounds". The bone-Pb "background" levels used here are low, and based upon a few observations only. However, they are in agreement with the low levels found in other studies of Scandinavians (Grandjean & Holma 1973; Lindh *et al.* 1978; Schütz *et al.* 1987a).

The present data on the retention of lead in blood a long time after end of occupational exposure support the direct observations of the lead retention in the skeleton, as this phase of the blood-Pb should mainly represent the skeleton.

A tri-exponential model for the lead retention in blood was significantly better than a bi-exponential model. We have strong evidence that the skeleton represents the slowest of these components while the fastest one corresponds to the blood and some soft tissues. As to the "intermediate" component, there is some other information indicating the presence of such a component, which may, at least partly, represent trabecular bone, and the slowest one then cortical bone. The turnover rate of the intermediate component resembles the fast bone-Pb component found in group A. The half-time of the intermediate component fits with other observations on turnover of trabecular bone lead (Schütz *et al.* 1987a). Furthermore, these data agree with the predictions of an earlier presented compartment model (Christoffersson *et al.* 1987).

The fact that blood-Pbs, even a long time after end of occupational exposure, were far above the "background", stresses the importance of "endogenous" lead exposure from the skeleton in lead workers.

The half-time of lead in the skeleton of more than a decade indicates that an accumulation will occur over several decades after a lasting increase in the exposure level. Thus, the skeletal lead level would be useful as an index of long-term exposure. Hence, *in vivo* measurements would be of great value in studies of associations between chronic exposure and effects.

There is a considerable variation in the individual estimates for the half-times of bone and blood lead. Other investigations have shown corresponding inter-individual difference in lead kinetics (Christoffersson *et al.* 1986; Schütz *et al.* 1987b). This observation is important, since it implies that some individuals, as a result of a certain degree of exposure to lead, may be at higher risk than others. The factors which govern these differences are so far unknown.

Conclusion

In conclusion the present data show: 1) A rather slow turnover of lead in the skeleton. 2) The usefulness of *in vivo* skeletal lead measurements as long-term exposure index. 3) The importance of bone as a source of "endogenous" lead exposure.

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Appendix 1.

Results of applying a mono-exponential model to describe the retention of lead in finger bone. Half-time is calculated from the estimated elimination rate; $T_1 = \ln 2/\lambda_1$, ∞ indicates $\lambda_1 < 0$. C_t is the estimated concentration at end of exposure, above the used "background" (3 $\mu g \cdot g^{-1}$).

Subject No.	Age [a] (y)	Exposure time (y)	Follow-up time [b] (y)	N[c]	C_t ($\mu g \cdot g^{-1}$)	T_1 (95% CI) (y)
A-1	65	38	7.2	11	62	27 (5.7,∞)
A-2	49	10	10.8	12	108	23 (11,1800)
A-3	57	22	8.8	12	61	6.2 (3.1,∞)
A-4	59	26	9.7	13	119	7.4 (5.0,15)
A-5	62	24	8.3	12	74	17 (6.9,∞)
A-6	65	14	9.8	16	49	6.6 (4.0,19)
A-7	65	33	10.1	17	102	15 (9.3,43)
A-8	65	26	9.9	15	131	15 (8.4,90)
Group A	64[d]	25[d]	9.8[d]	108	89[f]	13 (10.19)[e]
B-1	54	35	17.0	11	72	84 (9.7,∞)
B-2	30	3	18.5	13	71	15 (4.5,∞)
B-3	56	26	18.4	13	43	470 (9.9,∞)
B-4	65	45	13.2	7	49	∞ (45,∞)
B-5	41	10	16.9	11	21	∞ (8.9,∞)
B-6	51	34	18.3	12	124	11 (5.3,500)
Group B	53[d]	30[d]	17.7[d]	67	61[f]	37 (14,∞)[e]
Group A + B	58[d]	26[d]	10.4[d]	175	85[f]	16 (12,23)[e]

[a] At end of occupational exposure to lead.
[b] From end of occupational exposure.
[c] Number of measurements.
[d] Median.
[e] Shared half-time.
[f] Median intercept in the shared model.

Appendix 2

Results of applying bi- and tri-exponential models to describe the retention of lead in blood. Half-times are calculated from the estimated elimination rates: $T = \ln 2 / \lambda$. ∞ indicates $\lambda \leq 0$. C are the estimated concentrations at end of exposure, above the used "background" (0.38–0.56 μmol l^{-1}).

Subject No	N[a]	First component		Second component		Third component	
		C_1 (μmol l^{-1})	T_1 (95% CI)[b] (d)	C_2 (μmol l^{-1})	T_2 (95% CI) (y)	C_3 (μmol l^{-1})	T_3 (95% CI) (y)
A-1	18	0.28	6.0 (1.5,∞)	1.5	24 (16,47)	•	•
		–	–	–	–	–	–
A-2	46	3.1	46 (39,54)	1.9	7.9 (6.3,11)	•	•
		2.3	22 (17,32)	1.6	0.47 (0.32,0.91)	1.5	16 (10,38)
A-3	15	<0	30	1.2	5.2 (3.7,8.7)	•	•
		<0	30	1.4	3.6 (2.1,14)	0.002	∞
A-4	22	<0	30	1.6	11 (8.0,16)	•	•
		0.36	30	<0	2.4 (0.33,∞)	5.3	4.1 (0.67,∞)
A-5	18	1.7	30	1.4	107 (23,∞)	•	•
		1.1	30	1.2	8.9 (0.70,∞)	0.25	∞
A-6	25	0.53	30	0.88	7.1 (4.9,13)	•	•
		0.38	30	0.45	1.4 (0.32,∞)	0.54	26 (2.6,∞)
A-7	20	0.47	30	1.3	7.3 (5.4,11)	•	•
		0.53	30	1.4	11 (1.1,∞)	<0	∞
A-8	18	1.1	30	1.6	6.7 (5.2,9.7)	•	•
		0.83	30	1.3	4.0 (0.47,∞)	0.39	∞
Group A	182	0.30[f]	52 (46,60)[c]	1.5[f]	10 (9.0,12)[c]	•	•
		0.33[f]	31 (25,40)[c]	0.30[f]	0.84 (0.54,1.9)[c]	1.4[f]	12 (9.3,16)[c]
B-1	19	1.3	30	1.7	3.6 (2.8,5.1)	•	•
		0.69	30	6.6	1.3 (0,∞)	<0	1.3 (0,∞)
B-2	21	1.2	30	1.9	5.2 (4.7,5.9)	•	•
		1.1	30	1.8	2.8 (1.8,5.9)	0.23	∞
B-3	21	1.8	30	1.5	9.7 (8.5,11)	•	•
		1.2	30	1.1	0.70 (0.48,1.3)	0.93	19 (14,31)
B-4	13	1.0	30	1.7	11 (9.0,14)	•	•
		0.91	30	1.7	4.7 (1.6,∞)	0.13	∞
B-5	15	0.87	30	1.6	6.3 (5.3,7.8)	•	•
		0.86	30	<0	5.8 (0,∞)	1.8	6.3 (0,∞)
B-6	19	0.60	30	2.0	6.8 (6.0,7.8)	•	•
		0.16	30	1.3	1.2 (0.58,∞)	1.1	13 (8.0,30)
Group B	108	1.7[f]	224 (185,284)[c]	0.88[f]	15 (10,28)[c]	•	•
		0.91[f]	37 (24,86)[c]	1.3[f]	1.5 (1.0,3.2)[c]	0.82[f]	17 (11,38)[c]
Group A+B	290	0.78[f]	54 (47,62)[c]	1.5[f]	8.2 (7.6,9.0)[c]	•	•
		0.49[f]	34 (29,41)[c]	0.61[f]	1.2 (0.85,1.8)[c]	1.1[f]	13 (10,18)[c]

[a] Number of measurements.
[b] 30 days fixed, see text.
[c] Shared half-time.
[f] Median intercept in the shared model.
• Not applicable.
– Model did not converge.